Remarks

Rejection Under 35 U.S.C. § 112 ¶ 2

Claims 1, 4-7, 10-13, 16-22, 24, 25, 34, 62, and 64 stand rejected under 35 U.S.C. § 112 ¶ 2 as indefinite because the term "PSD95" is not defined. To advance prosecution, independent claim 1 is amended to recite "post-synaptic density 95 protein." Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (written description)

Claims 1, 4-7, 10-13, 16-22, 24, 25, 34, 62, and 64 stand rejected under 35 U.S.C. § 112 ¶ 1 as lacking adequate written description. Applicants respectfully traverse the rejection.

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). In this case, the Examiner contends that Applicant did not have possession of the genus antisense oligonucleotides recited in the pending claims.

The first step in a written description inquiry is to construe the claims properly. *Vas-Cath Inc.,* v. *Mahurkar*, 935 F.2d 1555, 1560, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). It is a fundamental rule of claim construction that every limitation is material and that what is claimed

is what is defined by the claim as a whole. *General Foods Corp. v. Studiengesellschaft Kohle GmbH*, 972 F.2d 1272, 1280, 23 U.S.P.Q.2d 1839, 1345 (Fed. Cir. 1992).

Each of independent claims 1, 7, 13, and 20 recites a genus of antisense oligonucleotides which are complementary to mRNA encoding human PSD95 and which inhibits expression of human PSD95. The Office Action contends that the claims define the recited antisense oligonucleotides only by function because the claims do not recite a sequence identifier. Paragraph bridging pages 4 and 5 of the Office Action. As an initial matter, a sequence identifier is not required when the claims recite a nucleic acid molecule which is well known in the art. The Court of Appeals for the Federal Circuit has held that an adequate written description of a nucleic acid molecule which is well known in the art does not require a structural recitation either in the specification or in the claims. *See Capon v. Eshhar*, 418 F.3d 1349, 1360-61, 76 U.S.P.Q.2d 1078, 1087 (Fed. Cir. 2005) ("the Board erred in ruling that § 112 imposes a per se rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field."). As explained in the response filed June 29, 2007, human PSD95 mRNA was known in the art before the May 12, 2000 priority date of this application. See GenBank Accession No. U83192, which was provided with the June 29, 2007 response.

The Office Action contends that the recited antisense oligonucleotides encompass not only those which are complementary to mRNA encoding human PSD95 but also "any such molecules with analogous human PSD95 activity, known or yet to be discovered . . . ." *Id.* There is no legal or scientific basis for construing the claims in this way. By the plain language of the claims, the recited antisense oligonucleotides are limited to those which are complementary to mRNA encoding human PSD95 and which inhibit expression of human

PSD95. Human PSD95 has a definite meaning in the art. See the paragraph bridging pages 1 and 2 of the specification; see also GenBank Accession No. U83192. Thus, the claims do not embrace antisense oligonucleotides which are complementary to "molecules with analogous human PSD95 activity, known or yet to be discovered" unless the antisense oligonucleotides meet the limitations of the claims; *i.e.*, are complementary to human PSD95 and inhibit expression of human PSD95.

Whether a specification meets the written description requirement is a question of fact. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). The analysis of the facts provided in Example 15 ("Antisense") of the PTO's Written Description Training Guidelines can be applied directly to the pending claims. Example 15 analyzed whether the following hypothetical claim met the written description requirement:

> An antisense oligonucleotide complementary to a messenger RNA having SEQ ID NO:2 and encoding human growth hormone, wherein said oligonucleotide inhibits the production of human growth hormone.

The pending claims meet the written description requirement for the same reasons the PTO determined that the hypothetical claim in Example 15 meets the requirement.

Compare the facts in this case with those in Example 15 of the PTO's Written Description Training Guidelines:

Example 15	**this application**
hypothetical claim: "An antisense oligonucleotide complementary to a messenger RNA having SEQ ID NO:2 and encoding human growth hormone, wherein said oligonucleotide inhibits the production of human growth hormone."	claims 1, 7, 13, 20: . . . an antisense oligonucleotide which is complementary to mRNA encoding human PSD95 and which inhibits expression of human PSD95 . . . .

"specification discloses a messenger RNA sequence, SEQ ID NO:1, which encodes full-length human growth hormone"	a nucleotide sequence (GenBank Accession No. U83192) that encodes full-length human PSD95 was known in the art before the May 12, 2000 priority date of this application
"specification states that the invention includes antisense molecules that inhibit the production of human growth hormone"	specification discloses that the invention includes antisense oligonucleotides that are complementary to mRNA encoding PSD95 and which inhibit expression of PSD95 (see page 6 ¶ 2)
"The general knowledge in the art is that any full-length complement of a target mRNA inhibits the function of the mRNA and is therefore an antisense oligonucleotide. Thus, one of skill in the art would view applicant's disclosure of a coding sequence, with the statement that the invention includes antisense oligonucleotides, as an implicit disclosure that the full-length complement of SEQ ID NO:1 is an antisense oligonucleotide."	GenBank Accession No. U83192 inherently describes a single species of oligonucleotide with a complete structure, *i.e.*, the full-length complement of U83192.
"In addition to the full-length complement, the genus includes fragments of the complement that retain antisense activity."	genus of antisense oligonucleotides recited in pending claims includes fragments that retain antisense activity
"It is generally accepted in the art that oligonucleotides complementary to a messenger RNA, including fragments of the full-length complement, have antisense activity when they match accessible regions on the target mRNA."	applies with equal force at May 12, 2000 priority date of this application[1]

[1] See Shuttleworth & Colman, *EMBO Journal* 7, 427-34, 1988 (cited in IDS accompanying this paper).

"Generally, the closer the complementary fragment is to full length, the greater the likelihood it will have antisense activity."	applies with equal force at May 12, 2000 priority date of this application[2]
"[O]ligonucleotides that retain complementarity to the Shine-Delgarno sequence usually have antisense activity."	applies with equal force at May 12, 2000 priority date of this application[3]
"The procedures for making oligonucleotide fragments of the SEQ ID NO:1 complement are conventional, e.g., any specified fragment can be ordered from a commercial synthesizing service."	applies with equal force at May 12, 2000 priority date of this application[4]
"The procedures for screening for antisense activity are also conventional, and the specification describes the assay needed to do gene walking."	procedures for screening for antisense activity, including "gene walking," were known in the art at this application's May 12, 2000 priority date[5]
"[T]he sequence provided in the specification defines and limits the structure of any effective antisense molecules."	prior art sequence GenBank Accession No. U83192 encoding human PSD95 defines and limits the structure of any effective antisense molecules: each such effective molecule must be complementary to an mRNA encoding human PSD95

Example 15 concludes that one skilled in the art would conclude that applicants were in possession of the invention in light of: (1) the specification's disclosure of the full-length sequence, which defines and limits the structure of any effective antisense molecules such that one skilled in the art would be able immediately to envisage members of the genus embraced by the claim, (2) the functional characteristics of the claimed invention as well as a routine art-recognized method of screening for antisense molecules which provide further distinguishing characteristics of the recited antisense molecules, and (3) the general level of knowledge and skill in the art.

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[2] See Stein & Cohen, *Cancer Res. 48*, 2659-68, May 15, 1988 (cited in IDS accompanying this paper).

[3] See Hirashima *et al.*, *J. Biochem. 106*, 163-66 (1989) (cited in IDS accompanying this paper).

[4] See Bjergård & Dahl, *Nucl. Acids Res. 19*, 5843-50, 1991 (cited in IDS accompanying this paper).

[5] See Parker *et al.*, *Nucl. Acids Res. 19*, 3055-60, 1991 (cited in IDS accompanying this paper).

The identical facts apply here, the only difference being that the full-length PSD95 coding sequence was known in the prior art and therefore not provided in the specification. This difference is irrelevant because, as explained above, an adequate written description of a nucleic acid molecule which is well known in the art does not require a structural recitation either in the specification or in the claims. *Capon v. Eshhar*, 418 F.3d at 1360-61, 76 U.S.P.Q.2d 1078 at 1087. Thus, as the PTO concludes in Example 15, the present specification adequately describes the recited genus of antisense oligonucleotides.

Whether the specification meets the written description requirement for the subject matter of claim 1 is a question of fact. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Thus, the M.P.E.P. requires a written description rejection to set forth express findings of fact. The express findings of fact must set forth two elements:

> In rejecting a claim, **the examiner must set forth express findings of fact** which support the lack of written description conclusion. These findings should:
>
> (A) Identify the claim limitation at issue; and
>
> (B) Establish a *prima facie* case **by providing reasons why** a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.

M.P.E.P. § 2163.04 ("Burden on the Examiner with Regard to the Written Description Requirement), internal reference omitted, emphasis added.

The rejection does not set forth express findings of fact to support element (B), a *prima facie* case. With respect to human PSD95 mRNA, the Office Action sets forth no evidence that the recited genus of antisense oligonucleotides is so varied that the specification does not describe it. Rather, the Office Action asserts that the genus "could not be envisioned by the

skilled artisan based on the disclosure of the specification." Page 9, lines 5-7. The Office Action provides no reasons at all why, in view of the disclosure of the application as filed, a person skilled in the art at the application's priority date would not have recognized that the inventors possessed the invention of claims 1, 4-7, 10-13, 16-22, 24, 25, 34, 62, and 64. In fact, the evidence of record is to the contrary. When the claims are properly construed, it is clear that the specification sufficiently describes the claimed subject matter.

Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (enablement)

The Office Action maintains the rejection of claims 1, 4-7, 10-13, 16-22, 24, 25, 34, 62, and 64 under 35 U.S.C. § 112 ¶ 1 as not enabled for their full scope. Applicants respectfully traverse the rejection.

As an initial matter, the Office Action contends that only intrathecal administration is enabled. Office Action at page 12. To advance prosecution, the claims have been amended to recite intrathecal administration.

The proper standard for determining whether the present specification meets the enablement requirement is whether any experimentation which may be needed to practice the methods of claims 1, 4-7, 10-13, 16-22, 24, 25, 34, 62, and 64 is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The Patent Office has not made a *prima facie* case that undue or unreasonable experimentation is needed to practice the claimed invention.

The Office Action acknowledges that the specification enables use of antisense oligonucleotides complementary to PSD95 mRNA and comprising SEQ ID NO:1 to relieve

acute or chronic pain, to treat or prevent hyperalgesia, and to reduce a threshold for anesthesia. Page 9, last paragraph. The amino acid sequence of human PSD95 protein available before May 12, 2000 is virtually identical to the amino acid sequence of rat PSD95 protein. See the ClustalW alignment of GenBank Accession Nos. U83192 (human), AAD56173 (human), and M96853 (rat) at the end of this response. Each of the human GenBank entries provided coding sequences for the PSD95 proteins. See U82392, provided with the June 29, 2007 response; and AAD56173 (under "CDS"), attached at the end of this response. In light of this evidence, it is not scientifically reasonable to contend that the mRNA molecules encoding the human and the rat proteins are so vastly different that the specification's examples using rat antisense oligonucleotides are not probative of enablement of human antisense oligonucleotides.

The Office Action cites Agrawal[6] as support for its assertion that the affinity of oligonucleotides depend on their base composition and sequence. Office Action at page 13. Agrawal actually provides guidance and speaks positively of the success of the antisense therapy: "Many questions about the effects of antisense oligonucleotide sequence . . . have been answered to a large extent, if not completely, in the past few years." Paragraph 1 of Agrawal's Concluding Remarks section, page 80. Also, Figure 3 of Agrawal provides guidance on improving specificity and pharmacokinetic profiles of oligonucleotides.

The evidence of record weighs heavily in favor of enablement. With the last response Applicants provided nine references that provided a sampling of the numerous clinical trials using a variety of antisense oligonucleotides that had been carried out and reported in the literature by the May 12, 2000 priority date of this application. In both the Final Office Action and the Office Action mailed September 25, 2007 the Examiner dismissed those references

[6] Agrawal *et al.*, *Mol. Med. Today 6*, 72-81, 2000.

because the references do not teach Applicants' invention. See page 17 ¶ 2 of the Final Office Action; and the paragraph bridging pages 16 and 17 of the September 25, 2007 Office Action. This is illogical. Moreover, the Examiner has not addressed Applicants' argument that by such logic, the Chirila,[7] Jen,[8] and Stein[9] references cited in the Office Action are also not relevant.

The Office Action has not made a *prima facie* case that claims 1, 4-7, 10-13, 16-22, 24, 25, 34, 62, and 64 are not enabled. Please withdraw the rejection.

Respectfully submitted,

BANNER & WITCOFF, LTD.

/Lisa M. Hemmendinger/

Dated: December 26, 2007 By: _____

Lisa M. Hemmendinger
Registration No. 42,653

Customer No. 22907

[7] Chirila *et al.*, "The use of synthetic polymers for delivery of therapeutic antisense oligodeoxynucleotides," *Biomaterials 23*, 321-42, 2002.

[8] Jen & Gewirtz, "Suppression of Gene Expression by Targeted Disruption of Messenger RNA: Available Options and Current Strategies," *Stem Cells 18*, 307-19, 2000.

[9] Stein, "Is irrelevant cleavage the price of antisense efficacy?" *Pharmacol. Therapeutics 85*, 231-36, 2000.

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Guide tree file	clustalw2-20071226-150500002.dnd
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SUBMIT ANOTHER JOB

To save a result file right-click the file link in the above table and choose "Save Target As".
If you cannot see the JalView button, reload the page and check your browser settings to enable Java Applets.

Scores Table

Sort by: Sequence Number | View Output File

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2	AAD56173	767	3	M96853	724	98

PLEASE NOTE: Some scores may be missing from the above table if the alignment was done using multiple CPU mode. Please check the output.

Sort by: Sequence Number | View Output File

Alignment

Show Colors | View Alignment File

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CLUSTAL W 2.0 multiple sequence alignment


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KEYWORDS    .
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  JOURNAL   J. Neurochem. 73 (1999) In press
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